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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,667	04/05/2005	Vasulinga Ravikumar	ISIS-5582	4970

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WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
11/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,667	RAVIKUMAR ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4 and 11-23* is/are pending in the application.

4a) Of the above claim(s) *19 and 21-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,11-18 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Election/Restrictions

Claims 19 and 21-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on September 18, 2006.

Claim Rejections - 35 USC § 102

The rejection over Rybakov et al. is withdrawn. While this reference does disclose a 5' phosphorylated oligonucleotide as noted in the figure legend, upon further review of the CAPLUS database record it is noted that the oligonucleotide's chemical name lists the 5' nucleotide as "2'-deoxycytidylyl", not "2'-deoxy-5'thiocytidylyl", indicating that this nucleotide lacks a 5' thio moiety.

Claim Rejections - 35 USC § 103

Claims 1, 4, 11-18 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uhlmann (US 6,033,909, of record) in view of Kostenko et al. (Nucleic Acids Research 2001, of record), Hamma et al. (Biochemistry 1999, of record) and Sproat et al. (Nucleic Acids Research 1987, of record).

Claim 1 is drawn to an oligomeric compound having the structure shown in the claim, having a phosphorothioate monoester at the 5' terminus wherein the phosphate is attached to a 5'-thionucleotide and comprising a hydroxyl or protected hydroxyl at the

3' terminus. Claim 4 recites that one position of the modified phosphate is methylated. Claim 11 states that R_1, R_2 and R_3 are each H, while in claim 12 they are each OH. Claim 13 states at least one of R_1, R_2 or R_3 may be an optionally protected substituent group, while claim 14 requires at least one optionally protected substituent group. Claim 15 states that each X_2 is S. Claim 16 defines heterocyclic base moieties that may exist within the oligomeric compound. Claims 17 and 18 state the length of the central portion of the oligonucleotide is between 8 and 30 or 15 and 25. Claim 20 is drawn to a composition comprising the oligomeric compound of claim 1 with a pharmaceutically acceptable carrier or diluent.

Uhlmann et al. teach oligonucleotides having formula 1 (see column 3). In this formula, the internucleotide linkages can be mono- or diphosphorothioate. The V at the 5' position of the ribose can be S and the terminal R^1 can be a phosphate group, which is the equivalent of the phosphorothioate monoester at the 5' terminus wherein the phosphate is attached to a 5'-thionucleotide of claim 1. The Z position of the terminal phosphate groups can be C_1-C_{18} alkyl, meeting the limitation of claim 4. In the oligonucleotides disclosed by Uhlmann et al., R^2 can be hydrogen, hydroxyl or other substituents, meeting the limitations of claims 11-14. Position B is disclosed as being a conventional nucleotide base, meeting the limitations of claim 16. The oligonucleotides of Uhlmann et al. are 2-101 nucleotides in length, meeting the limitations of claims 17 and 18 and are disclosed in claim 9 as compositions with pharmaceutically acceptable carrier or diluent, meeting the limitations of claim 20. Uhlmann et al. do not teach oligonucleotides having a hydroxyl or protected hydroxyl at the 3' terminus.

Kostenko et al. teach 5'-bis-pyrenylated oligonucleotides produced by conjugating pyrene to a 5' phosphorylated oligonucleotide for the purpose of producing a fluorescent probe that can quantitatively detect hybridization.

Hamma et al. teach that producing an oligonucleotide having a 5' phosphate allows a convenient "affinity handle" for purification by strong anion exchange HPLC. In view of these teachings, one of ordinary skill in the art would recognize that predictable synthesis of oligonucleotides having a 5' phosphate is routine and this technique is used for a variety of different reasons.

Sproat et al. teach the synthesis of 5'-mercapto-2', 5'-dideoxyribonucleoside phosphoramidites that can be used to produce oligonucleotides wherein the 5' oxygen is replaced with sulfur. Because these modified nucleotides are in a form suitable for automated nucleic acid synthesis, these monomers can be substituted at any position within an oligonucleotide, including the 5' terminus. Use of these monomers in a standard synthesis protocol produces oligonucleotides having 3' hydroxyls.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce oligonucleotides comprising 5' mercapto nucleotides and a 5' phosphate as taught by Uhlmann et al. and to make such an oligonucleotide comprising a 3' hydroxyl. Based on the teaching of Sproat et al. of 5' mercapto nucleoside phosphoramidites suitable for incorporation at any point in a synthetic oligonucleotide, one of ordinary skill in the art would recognize the use of this particular monomer to be a matter of simple substitution of known equivalents that would predictably provide 5' mercapto oligonucleotides. Based on the teachings of Kostenko et al. and Hamma et al. one of ordinary skill in the art recognizes that synthesis of 5'

phosphate oligonucleotides is routine in the art, therefore the synthesis of oligonucleotides comprising both a 5' mercapto nucleotide and a 5' phosphate is a matter of design choice made in the course of routine optimization using equivalent elements known to those of ordinary skill in the art.

Thus, the invention of claims 1, 4, 11-18 and 20 would have been obvious, as a whole, at the time the invention was made.

Response to Arguments

Applicants traverse the obviousness rejection by arguing that Formula I of Uhlmann et al. encompasses a large genus defined by the selection of a large number of Markush variables and one of skill in the art would not have selected a 5'-thiophosphate from this genus without some further motivation because Uhlmann et al. provides no teaching to specifically select the variable that provide a 5'-thiophosphate.

applicants' argument appears to be that the examiner is picking and choosing a large number of variables from Uhlmann et al. to arrive at the claimed compounds, however it is noted that in order to provide a 5' thiophosphate from Formula I one of ordinary skill in the art would have to choose only two variables, R^1 and V, and the variable V has only two possible choices. Even for R^1, the choices other than hydrogen fall into two classes of compounds: carbon chains such as would be used to tether additional compounds and a phosphate group. Because the number of variables and types of compounds defined by these variables is small, no additional teaching is needed in Uhlmann et al. to lead one to a 5' thiophosphate. Additionally, the rejection is based on references other than Uhlmann et al. that lead one of ordinary skill to choosing a phosphate as R^1.

Applicants argue with regard to the Kostenko and Hamma references that the instant claims do not embrace 5' phosphates and neither Kostenko et al. nor Hamma et al. teach or suggest 5' thiophosphates. It is correct that Kostenko et al. and Hamma et al. teach phosphates that are attached through an oxygen rather than a sulfur, but these references are relied upon to teach the advantages of the phosphate group, which are not expected to change based on how the phosphorus is attached to the oligonucleotide. Those in the art recognize that oxygen and sulfur are equivalent and interchangeable; as evidenced by Uhlmann et al., and applicants have presented no reasons why one would expect the possible uses for 5' phosphates would not also be applicable to 5' thiophosphates.

Applicants further argue that because Uhlmann et al. emphasize the benefits DNA probes with a 3' phosphate this reference teaches away from the claimed invention and thus Uhlmann et al. does not provide a motivation to prepare oligonucleotides with a 3' hydroxyl. This is not persuasive because teaching that oligonucleotides with 3' phosphates have some benefits does not constitute a teaching away from oligonucleotides without a 3' phosphate. Uhlmann et al. do not teach that one cannot produce oligonucleotides with a 3' hydroxyl or that such oligonucleotides would have no possible use.

With regard to Sproat et al., applicants argue this reference teaches a phosphoramidite that is added to an oligonucleotide to provide a free 5'- thiol group which can be coupled to a wide variety of reagents but does not teach or suggest that these phosphoramidite monomers can be substituted at any position within an oligonucleotide. While it is correct that Sproat et al. does not explicitly state these

monomers can be placed at any position within an oligonucleotide, those in the art familiar with oligonucleotide synthesis procedures recognize that the phosphoramidite monomers used in standard oligonucleotide synthesis procedures can be used at any position within an oligonucleotide.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

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Tracy Vivlemore
Primary Examiner
Art Unit 1635

/Tracy Vivlemore/
Primary Examiner, Art Unit 1635